

REMARKS

Reexamination and reconsideration in light of the foregoing amendment and the following remarks is respectfully requested.

Claims 1 and 54-75 are pending in this application. Claims 2-53 have been canceled. New claims 57-75 have been added. No new matter has been added to the application. Support for the amendments and the new claims can be found in the original claims and on page 4, lines 6-23; page 4, line 24 to page 5, line 2; page 6, lines 5-14 and 23-26; page 6, line 30 to page 7, line 2; page 8, lines 7-9; page 9, lines 3-8 and 21-24; page 12, lines 11-13; and page 16, lines 8-24.

Applicants note the Examiner's acknowledgment of Applicants' claim for foreign priority under 35 U.S.C. § 119 and receipt of the certified priority document. Applicants further note the Examiner's acceptance of the drawings filed December 17, 2002.

Applicants thank the Examiner for granting the interview on June 24, 2003. The interview provided a greater understanding of the Examiner's position with respect to the following rejections.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-23 and 54-56 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 2-23 have been canceled thereby rendering the rejection as to these claims moot. The Examiner at the interview indicated that the rejection comports with the guidelines set forth in the Trilateral Project WM4 "Report on comparative study on protein 3-dimensional (3-D) structure relating claims" and that the claims need to be restructured to overcome this rejection.

Claim 1 has been amended to recite a method of identifying a compound as opposed to designing or selecting a compound. Claim 1 has been further amended to require that the method is directed to identifying a compound that modulates (i) binding of a natural ligand to the EGF receptor, ErbB3 or ErbB4 or modulates signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4, and then (ii) testing the compound's ability to modulate binding or signal transduction thereof.

Applicants' position is that the level of skill of those working in the field of *in silico* screening at around the priority date of the present application (i.e., around May 1998) was relatively high. More specifically, the average capabilities of those working in this field included the ability to identify candidate binding pockets within any given 3D structure using standard methodologies.

Computer algorithms that may be used for this purpose, include, for example, PASS (evidence: Brady, G.P., Jr. et al., "Fast prediction and visualization of protein binding pockets with PASS," *J. Comput Aided Mol. Des.*, vol. 14, 383-401 (2001); copy attached as Exhibit A). The PASS algorithm involves coating the surface of the protein structure model with sets of probe spheres, retaining those with low solvent accessibility and identifying some of these as likely centers of binding pockets. A person skilled in this field would have been fully familiar with the implementation of a range of docking programs (such as those listed in the patent application) to screen for candidate binding ligands. Evidence of the techniques that would be well within the capabilities of those skilled in this field are described in the following publications:

(1) Li et al., "Structure-based design of parasitic protease inhibitors," *Bioorg Med Chem*, 1996 Sep, 4(9):1421-7. Copy attached as Exhibit B.

(2) Ring et al., "Structure-based inhibitor design by using protein models for the development of antiparasitic agents," *Proc Natl Acad Sci USA*, 1993 Apr 15, 90(8):3583-7.

Copy attached as Exhibit C.

(3) Li et al., "Anti-malarial drug development using models of enzyme structure," *Chem Biol.*, 1994 Sep, 1(1):31-7. Copy attached as Exhibit D.

As mentioned above, Applicants submit that any competent researcher working in the field of *in silico* screening would be able to identify candidate binding pockets in any given 3D structure. In the present case, however, the patent application actually identifies specific "topographic regions" which represent preferred "binding pockets" within the EGFR structure. These binding pockets can be used in screening methods to identify potential ligands and are described as follows:

(i) The fragment which includes residues 1-475 of the receptor, comprises the L1, S1 and L2 domains of the ectodomain of the EGF receptor. At the center of the structure is a cavity, bounded by all three domains, of sufficient size to accommodate a ligand molecule (see the specification at page 5, lines 5-7).

(ii) The fragment, which includes residues 313-621 of the receptor, comprises the L2 and S2 domains, which are positioned such that they form a "corner" structure. It is envisaged that this corner structure provides a further binding site for ligands of EGF receptor family members (see the specification at page 5, lines 8-11).

The patent application provides further guidance for selecting regions within the identified binding pockets at page 5, line 25 to page 6, line 22. For example, it is stated that the ligand may interact with (i) a region of the L1 domain-S1 domain interface thereby causing an alteration in the positions of the domains relative to each other; (ii) a hinge region between the

S1 domain and the L2 domain causing an alteration in the positions of these domains relative to each other; or (iii) the β -sheet of the L1 domain causing an alteration in the position of the L1 domain relative to the position of the S1 domain or L2 domain.

The patent application goes even further by specifying two sites on the lower β -sheet of the L1 and L2 domains as suitable targets for screening. See, for example, the specification at page 6, lines 9-14.

Accordingly, the patent application not only identifies the binding pockets within the EGFR structure, but suggests preferred regions within these binding pockets to use in screening for ligands.

Armed with the atomic coordinates of the EGF receptor provided in the patent application and the information regarding preferred regions within specified binding pockets, it would have been a matter of routine for a person skilled in the area of *in silico* screening to utilize any one of the well known docking programs to screen for potential ligands.

On page 3 of the Office Action, the Examiner states that it is unknown and cannot be predicted from the information presented in the specification what degree of stereochemical complementarity is required. Stereochemical complementarity between a chemical compound and the target protein structure is a cumulative effect of the hydrogen bonds, favorable electrostatic interactions, and favorable van der Waals contacts between the compound molecule and the protein molecule. Depending on the nature of the compound molecule, one factor may predominate over others in contributing to the overall complementarity. Those skilled in the art can visually examine on a computer graphics monitor a compound molecule docked into the binding site of the receptor and assess the source of the complementarity. All docking programs

have scoring functions which are used to dock and then rank the molecules with a score indicating how well a particular chemical compound molecule binds to the receptor.

The top-ranking compounds can then be further assessed visually and computationally. For example, a computer program such as XSCORE (evidence: Wang, R. et al., "Further development and validation of empirical scoring functions for structure-based binding affinity prediction," *J. Compu Aided Mol. Design*, Vol 16, 11-26(2002); copy attached as Exhibit E) has a scoring function which predicts the dissociation constant for a given ligand-protein complex structure (for example, the docked compound-receptor complex). This scoring function was derived by fitting the function to the experimentally determined dissociation constants of a set of 200 ligand-protein complexes. As a general rule, stereochemical complementarity is not discussed in terms of degree. *In silico* screening requires certain parameters to be set to determine whether or not any given molecule will register as a stereochemical "fit" with the binding site of interest. A person of skill in this area would be able to set appropriate parameters through trial and error to select for suitable stereochemical complementarity to a binding site described in the patent application.

On page 3 of the Office Action, the Examiner points out that claim 1 requires that the selected compound bind to any molecule of the EGF receptor family and modulate any activity mediated by the molecule. Amendments have been proposed to claim 1 to make it clear that the compound is tested for its ability to either modulate binding of a natural ligand to EGF receptor, ErbB3 or ErbB4 or to modulate signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4. We submit that these amendments obviate this aspect of the Examiner's rejection.

On page 4 of the Office Action, the Examiner asserts that the specification provides no guidance on how to use "one or more subsets of said amino acids related to the coordinates

shown in Figure 6 by whole body translations and/or rotations." Applicants respectfully submit, however, that the specification provides adequate guidance for selecting regions within the identified binding pocket (i.e., specific subsets of amino acids) throughout the description at page 5, line 25 to page 6, line 22 (see also the comments above).

For all of the foregoing reasons, the specification provides sufficient guidance that a person having ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, claims 1 and 54-56 satisfy the requirement of 35 U.S.C. § 112, first paragraph. It is respectfully requested that the rejection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-23 and 54-56 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner objected to language specifically recited in claims 1-12 and 14. Claims 2-23 have been canceled thereby rendering any rejection under 35 U.S.C. § 112, second paragraph, as to these claims moot.

In claim 1, the Examiner objected to the phrase "assessing the stereochemical complementarity between the compound and a topographic region of the molecule" in that she did not know "what delimits a topographical region." The language "a topographical region" has been deleted from the claim. It is believed that by this amendment, the rejection is overcome.

Also in claim 1, the Examiner objected to the phrases "substantially as shown" and "forms an equivalent." With respect to the term "substantially," Applicants submit that a person skilled in the art would have understood that the coordinates set out in Figure 6 need not be strictly adhered to in order to generate a three dimensional structure *in silico* for screening for ligands of the EGF receptor, ErbB2, ErbB3 or ErbB4. See Section 2173.05(b) of MPEP, and in

particular, the discussion on the term “substantially.” This Section refers to a decision in which the phrase “which produces substantially equal E and H plane illumination patterns” was considered definite because one of ordinary skill in the art would know what is meant by “substantially equal”. *Andrew Corp v Gabriel Electronics*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988). In the present case, given the nature of the invention and the experience of those skilled in the art of *in silico* screening, the phrase “substantially as shown in Figure 6” in relation to coordinates would have been clearly understood. Applicants also point out that this phrase is present in a method claim which involves numerous steps including obtaining a compound with requisite stereochemical complementarity and testing the compound for its ability to modulate binding of a natural ligand to EGF receptor, ErbB3 or ErbB4 or signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4. Within the context of this screening process, a person skilled in the art would understand the flexibility in variation from the exact coordinates shown in Figure 6 which would allow generation of a structure with sufficient identity to the EGF receptor coordinates listed in Figure 6 to allow screening for ligands.

With respect to the phrase "forms an equivalent", this phrase has now been amended to refer to an amino acid sequence of ErbB2, ErbB3 or ErbB4 that forms an equivalent structure to that formed by amino acids 1-621 of the EGF receptor. In light of the information provided in the specification, and in particular, the sequence alignment information provided in Figures 1 and 2, a person skilled in the art would have clearly understood what is meant by this phrase.

For all of the foregoing reasons, it is respectfully requested that the rejection of claim 1 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-23 and 54-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hendry et al. (U.S. Patent No. 5,705,335). Claims 2-23 have been canceled thereby rendering the rejection as to these claims moot.

The Examiner finds that the claims are obvious in light of Hendry et al. This reference relates to a computer based method for creating a pharmacophore which involves determining the optimal fit of compounds into nucleic acid sequences such that the lowest energy of interaction and best steric fit are obtained. In support of this rejection, the Examiner refers to the Trilateral Project WM4 "Report on comparative studies on protein 3-dimensional (3-D) structure related claims." This report states that if the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functionally descriptive or non-functionally descriptive material.

Applicants submit that the difference between amended claim 1 and the prior art is not merely limited to descriptive material stored or employed by a machine, i.e., step (A) of assessing stereochemical complementarity between a compound and the 3-dimensional structure of a molecule of the EGF receptor family, but it also involves step (B) of obtaining a compound which possesses stereochemical complementarity to the molecule; and step (C) of testing the compound for its ability to (i) modulate binding of a natural ligand to the EGF receptor, ErbB3 or ErbB4, or (ii) modulate signal transduction via the EGF receptor, ErbB2, ErbB3 or ErbB4. Steps (B) and (C) of claim 1 are clearly not merely descriptive material stored or employed on a machine. These steps involve physical testing of compounds for their ability to modulate a specified activity of a member of the EGF receptor family.

Hendry et al. do not disclose or suggest a method of screening for a compound which binds to a molecule of the EGF receptor family followed by testing of compounds identified for their ability to modulate either binding of natural ligands or signal transduction via a member of the EGF receptor family. It is respectfully submitted, therefore, that claims 1 and 54-56 as amended are clearly novel and non-obvious over the prior art.

For all of the foregoing reasons, the Examiner has not established a *prima facie* case of obviousness. It is respectfully requested that the rejection be reconsidered and withdrawn.

NEW CLAIMS

New claims 57-75 are presented for examination. Claims 57-72 are ultimately dependent on base claim 1. For the reasons set forth above for patentability of claim 1, it is believed that new claims 57-72 are allowable. New claim 73, and its dependent claims, claims 74 and 75, is directed to the method steps (A) and (B) as in claim 1, but requires in step (C) of "selecting a compound that has a K_d or K_i of less than 10^{-6} for a molecule of the EGF receptor family selected from the group consisting of the EGF receptor, ErbB2, ErbB3 and ErbB4." The reference relied upon by the Examiner does not teach or suggest step (C) as required by claim 73. For all of the foregoing reasons, it is believed that claims 57-75 are patentable.

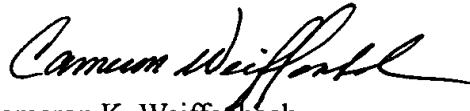
Conclusion

It is submitted that the claims 1 and 54-75 are patentable over the teachings of the prior art relied upon by the Examiner as well as comply with the requirements of 35 U.S.C. § 112, first and second paragraphs. Accordingly, favorable reconsideration of the claims is requested in light of the preceding amendments and remarks. Allowance of the claims is courteously solicited.

A petition for a three-month extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT, WILL & EMERY



Cameron K. Weiffenbach
Registration No. 44,488

600 13th Street, N.W.
Washington, DC 20005-3096
(202) 756-8000 CKW:ckw
Facsimile: (202) 756-8087
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